LEVOTHYROXINE SODIUM TABLETS

An FDA Overview from the CMC Standpoint

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Joint Public Meeting on Equivalence of Levothyroxine Sodium Products

Co-sponsored with the FDA by the American Thyroid Association, The Endocrine Society and the American Association of Clinical Endocrinologists

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National Transportation Safety Board

L'Enfant Plaza

Washington, DC

Outline

- Description
- History
- Regulatory History
- Current status

Levothyroxine drug products

- Active substance is an endogenous thyroid principle, designated as T_4.
  - Half-life of T_4 is approximately 7 days
- Formulated as immediate-release tablets
  - Manufactured via compression
  - In vitro dissolution characteristics vary

History

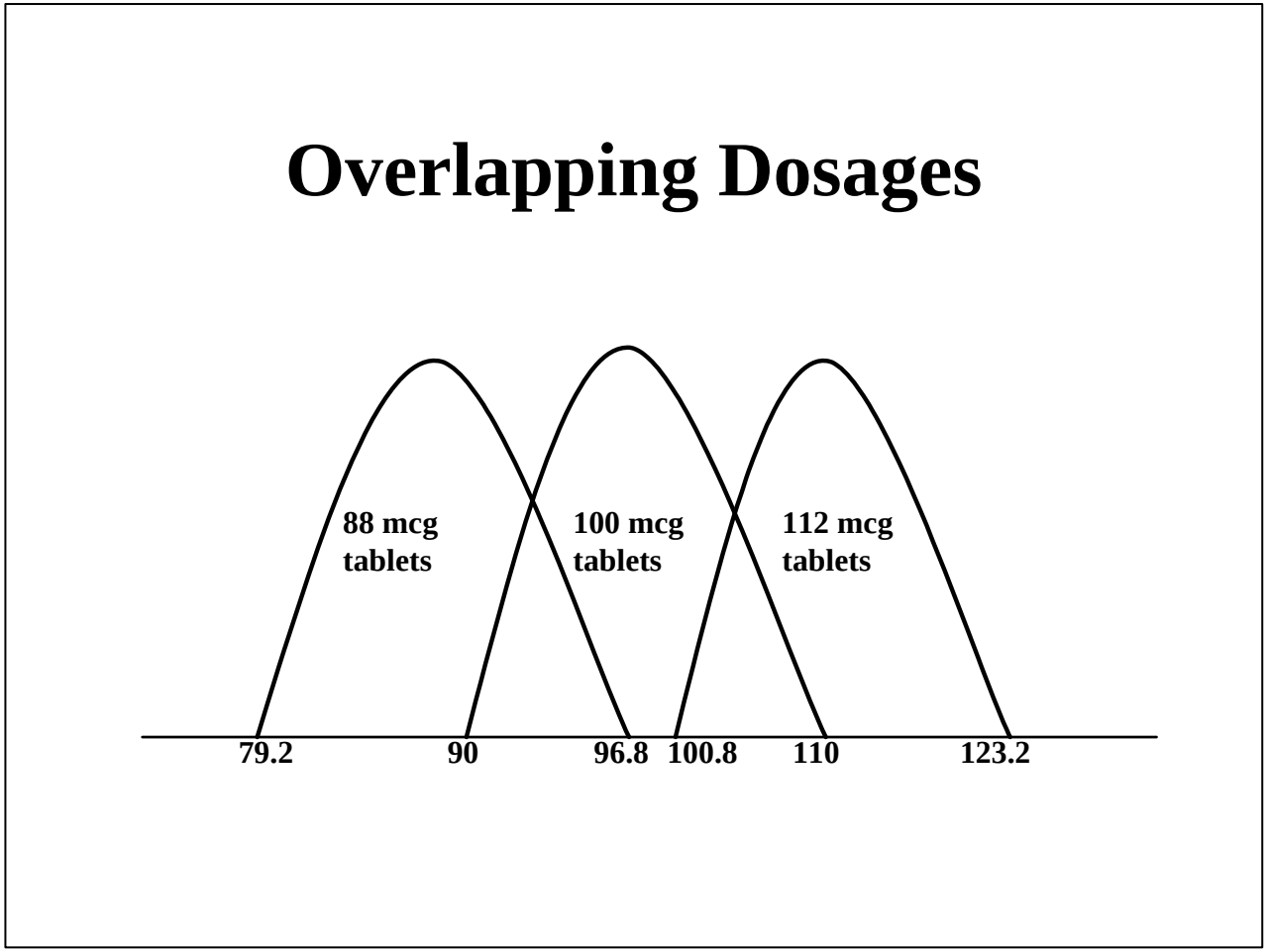
- Levothyroxine (T_4) drug products marketed without NDA from the 1950's until 2001
  - Products were often chemically unstable.
  - Formulated with > 100% labeled claim of T_4.
  - Some lost as much as 20% of initial T_4 during expiry.
  - Degradation products not monitored.
  - No standardized specifications/protocols.
  - Inconsistent quality

Inconsistent quality

- Non-NDA (pre-1997) T_4 tablets exhibited poor consistency and uniformity
  - Product – to – product
  - Batch – to – batch
    - **Some tablet strengths could overlap upon degradation**, *e.g.*, a superpotent 100-mcg tablets could contain more T_4 then a degraded 112-mcg tablet
  - Within batch, tablet – to - tablet

Example of poor batch consistency

[Simulated Data]



Regulatory History

- T_4 drug products were designated as new drug products
  - File NDA applications (62 FR 43535, 14 Aug 1997)
  - Deadline extended to 14 Aug 2001 (65 FR 24488)
  - FDA's Enforcement Guidance to Industry
    - CMC requirements (filing, stability)
    - Enforcement of compliance date and submission of new drug applications

Current Status

- FDA received NDAs for T_4 drug products
  - Seven were approved (4 currently marketed in the USA)
- All applications received after 14 Aug 2001 were ANDAs (generic applications)

Current status- manufacturing

- Most were reformulated to:
  - **TARGET 100% LABELED CLAIM (LC) AT RELEASE**
  - **ESTABLISH CONTENT UNIFORMITY AROUND 100%**
  - Exhibit adequate stability when tested at ICH conditions of 25ºC and 60% RH

Current status - quality

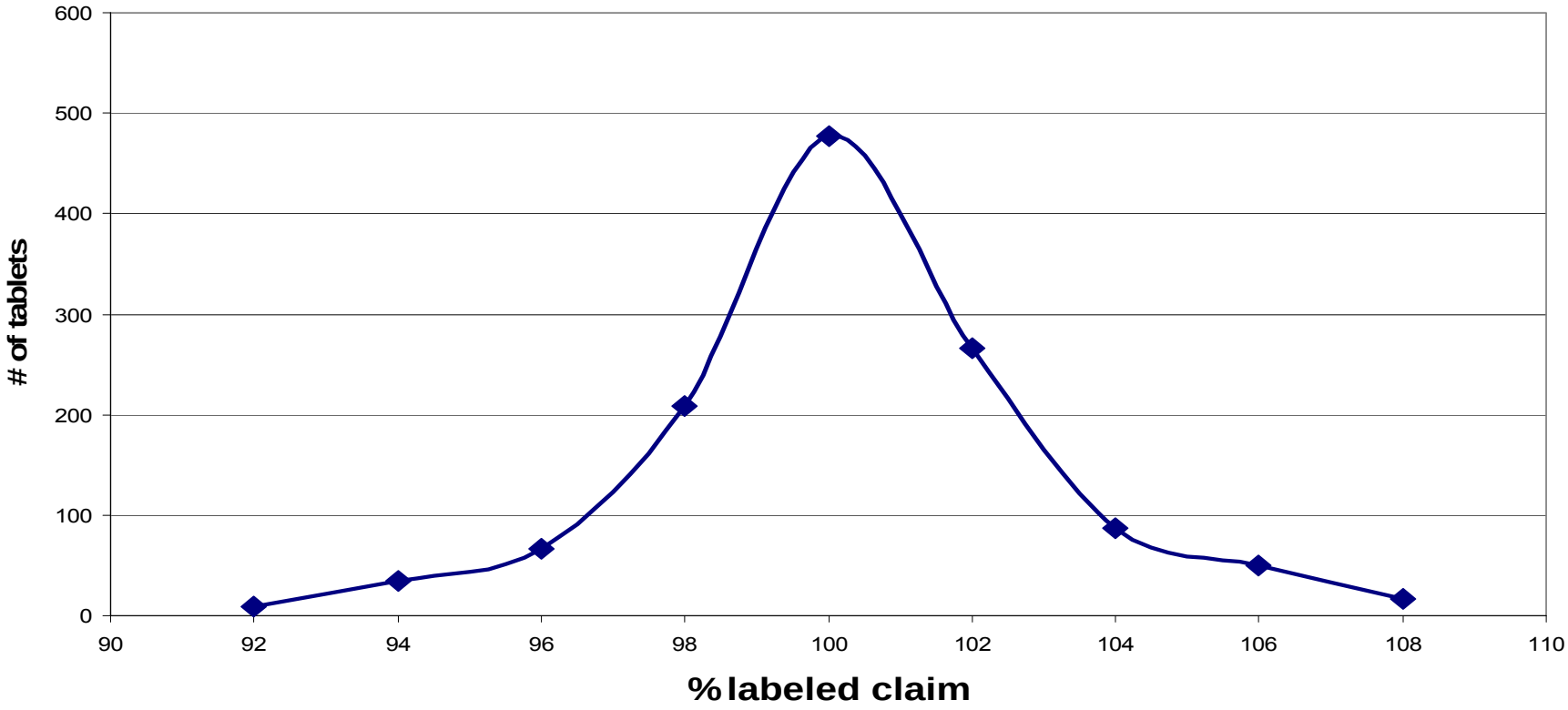
- All NDAs were reviewed to the same standards
  - CMC review of drug substance manufacture via DMF
  - Drug product released at 100% LC
  - Degradation products monitored
  - Uniform stability protocol
    - ICH stability storage conditions
    - Loss of drug substance ≤ 10% of initial

Current status - specifications

- Assay: 90.0 – 110.0% by HPLC
  - ***Target is 100%***, range to accommodate variability in manufacturing process and analytical methodology
- Dissolution: Monograph tests 1, 2, or 3
- Content uniformity: USP <905> or tighter
- Identification: TLC
- Degradation products: validated HPLC method
- Miscellaneous
  - Hardness, moisture, friability

Content uniformity

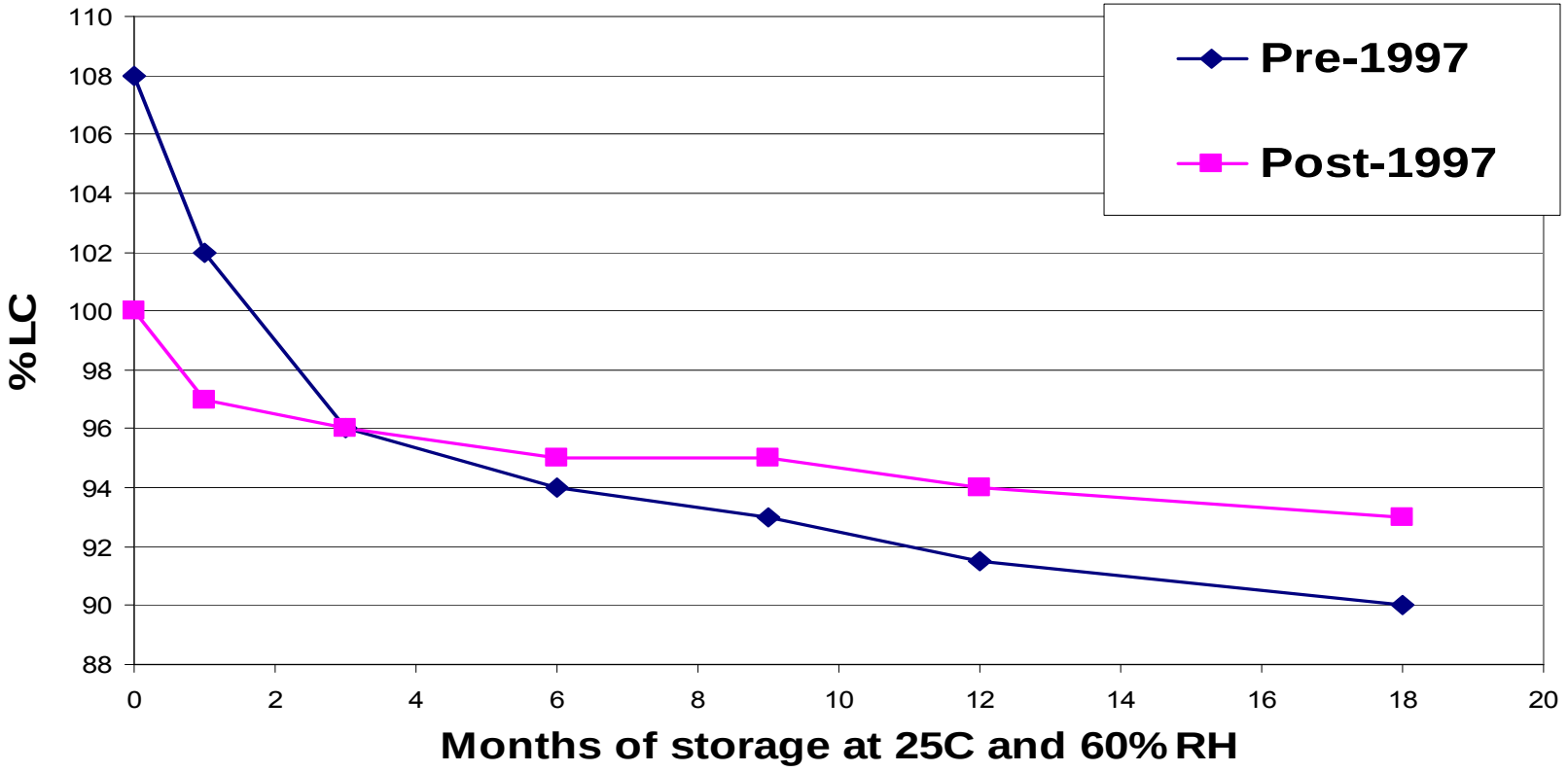
[Simulated Data]



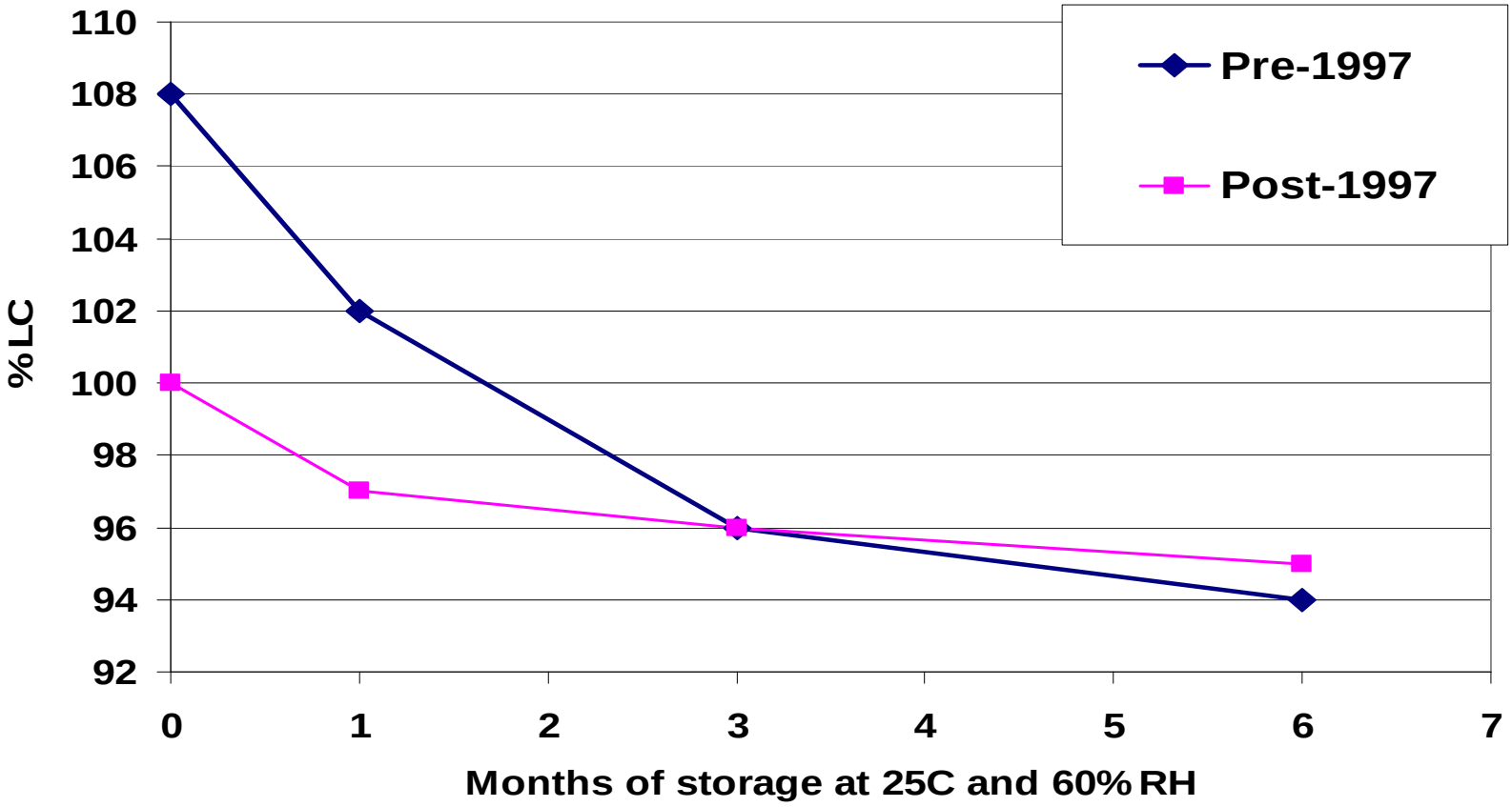
Current status - stability

- T_4 drug products are tested according to ICH Q1A
  - Q1A: designates storage conditions, recommends testing frequency

Comparison of pre- and post- FR notice T4 drug products



Comparison of 1st 6 months



Acknowledgement

David B. Lewis, PhD